Mesothelioma:
The standard of care

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take home messages PILC 2006

- All patients should receive adequate palliation of dyspnea and pain before starting chemotherapy
- Fit patients should be considered for palliative chemotherapy with platinum/antifolate for 4-6 cycles or even more in case of good response
- Sensitive patients should at relapse be considered for retreatment with chemotherapy
- Radical treatment should only be considered as part of a clinical trial in experienced institutions

the standard of care 2009

- **Palliative**
  - **Radiotherapy**
  - **Chemotherapy**
- Supportive care
- Radical treatment
  - Surgery w/wo chemo and /or radiotherapy
- Targeted therapy

- New evidence
  - Published studies >50 pts, since 2006
  - IMIG, 2008
- Statement
  - BTS, *Thorax 2007*
- Guidelines
  - ESMO, *Ann Oncol 2008*
  - ERS-STS, *ERJ 2009*

palliative radiotherapy

- No RCT; 1 systematic review (*Ung, 2006*)
- Retrospective and uncontrolled series
  - Palliative radiotherapy provides pain relief in about half of all patients for a median duration of 2-3 m
  - Small volumes, short schedules preferable
  - More effective if bone erosion or subcutaneous masses; less effective for diffuse pain and for retreatment
  - Rarely effective for breathlessness and superior vena caval obstruction
  - No data on QOL

guidelines (1)

- ESMO: Conventional radiotherapy dose can be delivered locally as a palliative measure for pain management
- ERS-STS: Palliative radiotherapy aimed at pain relief may be considered in cases of painful chest wall infiltration or nodules (2C)

Eur Respir J 2007; 30: 1021–1025
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CORRESPONDENCE

Drain site radiotherapy in malignant pleural mesothelioma: a wasted resource

Prophylactic Irradiation of Tracks (PIT)

RCT	N	RT	f/up	Tract metastasis	p
Boutin 1995	40	7 Gy d 1-3 12.5-15 Mev	Mean 6 m	40 vs. 0%	< 0.001
Bydder 2004	58	10 Gy d1 9 Mev		7 vs. 10%	0.53
O'Rourke 2007	61	7 Gy d 1-3	Median 8 m	10 vs. 13%	0.75
Poor man's meta-analysis	159	Absolute risk reduction: 11 (5-22)		NNT: 9	

PIT currently advocated by 84% of Belgian-Dutch RT services (*De Ruysscher 2004*)

Prophylactic irradiation of tracks

Table 1
Randomized controlled trials of radiation therapy for MPM

Reference	Diagnostic/ palliative procedures	Prophylactic EBRT (dose & fx)	N	Median survival	Procedure tract metastases	Adverse effects
Boutin et al. [5]	Thoracoscopy	21 Gy in 3Fx	20	14 mo	0%[a]	No patients with inflammation or edema
		No EBRT	20	8 mo	40%[a]	NA
O'Rourke et al. 2007	Thoracic drain, pleural biopsy or thoracoscopy	21 Gy in 3Fx	31	8 mo	13%	NR
		No EBRT	30		10%	NA
Bydder et al. [8]	FNA, Abrams needle biopsy, thoracoscopy, or thoracic drain	10 Gy in 1Fx	43 total[c]	8.7 mo 1 year: 35%	7%[c,d]	No patients with RTOG/EORTC Grade 2–4 toxicities
		No EBRT		NR	10%[c,d]	NA

Relative Risk: 0.47, 95% CI 0.01–30.90, p = 0.72) *Ung,2006*

guidelines (2)

- ESMO: Prophylactic radiotherapy to reduce the incidence of port metastases is controversial and not routinely applied
- ERS-STS: The value of prophylactic radiotherapy is questionable. Therefore the experts were not able to draw any recommendation

palliative chemotherapy

- Appropriate?
- If appropriate,
  - Which regimen?
  - Which dose?
  - When to initiate?
  - Optimal duration?
  - Which salvage?

appropriate?

Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial

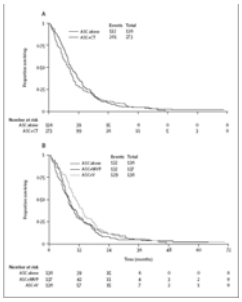
Marion F Muers, Richard J Stephens, Patricia Fisher, Liz Darlison, Christopher M B Higgs, Erica Lowry, Andrew G Nicholson, Mary O'Brien, Michael Peake, Robin Rudd, Michael Snee, Jeremy Steele, David J Girling, Matthew Nankivell, Cheryl Pugh, Mahesh K B Parmar, on behalf of the MS01 Trial Management Group*

Summary

Background Malignant pleural mesothelioma is almost always fatal, and few treatment options are available. Although Lancet 2008; 371: 1685–94

Supportive care can be very active

- MS 01 (*Muers, 2008*) randomisation:
- ASC:
  - regular follow-up in a specialist clinic
  - structured physical, psychological, and social assessments at every clinic visit
  - rapid involvement of additional specialists and parallel nursing support
  - as required, steroids, analgesic drugs, appetite stimulants, bronchodilators, or palliative radiotherapy
- 3 weekly $MVP_{50\ mg/m^2}$ x 4
- weekly vinorelbine x 12



Supportive care can be very active (2)

- Comparative chemotherapy not adequate
  - No or insufficient dose of cisplatin
  - 12 w of treatment
- Trial prematurely stopped and underpowered
  - Difficulty of conducting RCT's with SC-only arm
  - Trend towards efficacy of vinorelbine
- Overall median survival in ASC of 7.6 m
  - Suggests poor prognostic group
  - Due to delay in treatment of median 2 m after D.
- JMCH (Pemetrexed) & EORTC (Raltitrexed) trials
  - Activity of cisplatin only control arm considered ≥ 'no chemo'
  - Any significant improvement seen with the addition of antifolate to cisplatin likely to be also applicable to 'no chemo'

which regimen?

- How many drugs in 1st line?
- Platinum-no platinum combination?
- Which platinum?
- Which combination?

how many 1st line drugs?

			No. pts.	Survival		
	Author	Regimen		ORR %	1 yr%	median mths
1	JMCH, 2003	CDDP	222	17	38	9
	EORTC, 2005	CDDP	124	14	40	8.8
	Taylor, 2008	PTX	247	11	59	14.1
	Talbot, 2007	Vinflunine	67	14		10.8
	Muers, 2008	Vinorelbine	136	16*	42	9.5
2	JMCH, 2003	Pemetrexed + CDDP	226	41	50	12.1
	EORTC, 2005	Raltitrexed + CDDP	126	24	46	11.4
3	Muers, 2008	MVP	137	10*	31	7.6
	Hillerdal, 2008	Gemc + CBDCA + Caelyx	173	32	52	13.0

* Not in he ITT population

platinum vs. non-platinum combo?

Author	Regimen	No. pts.	Survival		
			ORR %	1 yr%	median mths
JMCH, 2003	Pemetrexed + CDDP	226	41	50	12.1
EORTC, 2005	Raltitrexed + CDDP	126	24	46	11.4
Janne, 2008	Gemc + Pemetrexed	56	26	31	8
	(randomized phase 2)	52	17	46	10

which platinum?

Author	Regimen	No. pts.	Survival		
			ORR %	1 yr%	median mths
JMCH, 2003	Pemetrexed + CDDP	226	41	50	12.1
EORTC, 2005	Raltitrexed + CDDP	126	24	46	11.4
Sørensen, 2008	Vinorelbine + CDDP	54	29	61	16.8
Santoro, 2008	Pemetrexed + CDDP	745	26	63	11
	Pemetrexed+ CBDCA	752	22	64	NA
Ceresoli, 2006	Pemetrexed+ CBDCA	102	19	NA	12.7
Hillerdal, 2008	Gemc + CBDCA + Caelyx	173	32	52	13.0

which 2nd drug?

Author	Regimen	No. pts.	Survival		
			ORR %	1 yr%	median mths
JMCH, 2003	Pemetrexed + CDDP	226	41	50	12.1
EORTC, 2005	Raltitrexed + CDDP	126	24	46	11.4
Karrisson, 2007	Gemc + CDDP	55	22	31	15
Sørensen, 2008	Vinorelbine + CDDP	54	29	61	16.8

guidelines ESMO (3)

- The combinations of both pemetrexed/ cisplatin and raltitrexed/cisplatin have been shown to improve survival as well as lung function and symptom control in comparison with cisplatin alone in randomized trials *[II,A].*
- The combination of pemetrexed with carboplatin is an alternative effective therapy *[III, A]*

guidelines ERS-STS (4)

- When a decision is made to treat patients with chemotherapy alone, patients in a good performance status should be treated with first line combination chemotherapy consisting of platinum and pemetrexed or raltitrexed (1B)

other issues

- **Which dose?**
  - MTD of pemetrexed/cisplatin was obtained w/o vitamins
  - 2 randomised dose escalation trials in 2nd line NSCLC show no dose –response relationship *(Cullen 2007, Ichinose 2007)*
- **When to initiate?**
  - RMD trial: immediate chemotherapy vs.delayed (*O'Brien, 2006)*
  - 43 good PS pts with stable symptoms
  - MST 14 m vs. 10 m (NS but small sample size)

other issues (2)

- **Optimal duration of chemotherapy?**
  - *JMCH*: median 6; *EORTC*: median 5
  - Continuing responses after 4-6 cycles repeatedly reported
- **Maintenance?**
  - *vd Bogaert 2006,* non-randomised
  - 13/27 pts continued on pemetrexed after 6 induction cycles
  - 3/13 had continuing response; median survival of maintenance pts 18m

guidelines ERS-STS (5)

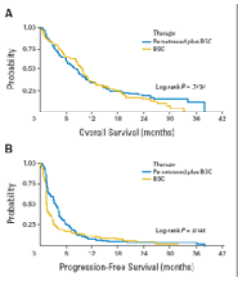
- Administration of chemotherapy should not be delayed and should not wait for the appearance of functional clinical signs (1C).
- Chemotherapy should be stopped in case of progressive disease, grade 3-4 toxicities, or cumulative toxic doses (1A), or following up to six cycles in patients who respond or are stable (2C)

which salvage treatment?

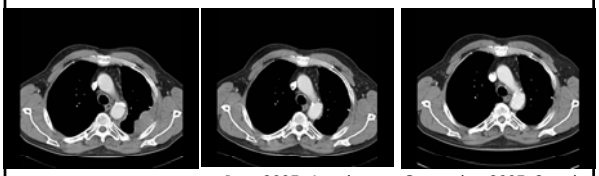
		No. pts.	Survival		
Author	Regimen		ORR %	1yr %	OS mths
Manegold, 2005	PTX-CDDP-> no salvage	142	NA	NA	9.8
	CDDP->no salvage				6.8
	PTX-CDDP-> any salvage	84			15.3
	CDDP->any salvage				12.2
Jassem, 2008	BSC	120	2	37	9.7
	BSC + Pemetrexed	123	19	38	8.4
Janne, 2006	PTX	91	6	35	4
	PTX + CDDP	96	33	25	7.6
Taylor, 2008	PTX	396	12	55	NA
Zucali, 2008	Gemc + VNB	30	10		10.9

salvage chemotherapy (2)

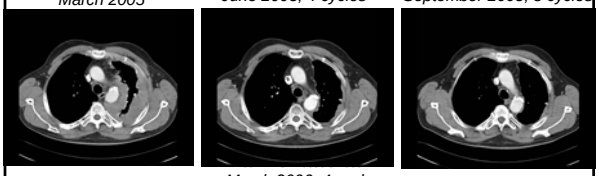
- *Jassem, 2008*
- BSC +/- pemetrexed in pretreated pts
- Exploratory analyses adjusting for imbalance in number and interval to post-discontinuation treatment shows improved OS



retreatment



March 2005 | *June 2005, 4 cycles* | *September 2005, 8 cycles*



January 2006 | *March 2006, 4 cycles* | *July 2006, 8 cycles*

guidelines ERS-STS (6)

- Patients demonstrating prolonged symptomatic and objective response with first line chemotherapy may be treated again with the same regimen in the event of recurrence (2C)
- In other cases, inclusion of the patients in clinical trials is encouraged (2C).

personal conclusions

- Any platinum-3rd generation combination likely to be active in selected patients with advanced mesothelioma
- Antifolate to be considered in antifolate-naive relapsing pts
- Select your patient!
  - Good PS (WHO 0-1); fit for combination chemotherapy
  - No prior cancer or chemotherapy
  - Few data on 75+ patients
- Non-epitheloid subtype: no evidence for being predictive for absence of benefit

chemotherapy vs. surgery

TABLE 5. Some Studies Where Surgery and/or Multimodality Therapy Has Been used Compared to the Present Study

Reference	Treatment	Subtypes, n	Median Survival, mo	Comments
Hillerdal, 2008	Carbo-gemc-caelyx,	All, 173	13	
		EP, 116	17	
		EP, stage 1–2, PS 0–1, <70 y	22	
	EPP + RT + C		29	Those who survived surgery only
22	EPP + RT	All, 61	17	
23	EPP + RT	All, 26	18	Perioperative deaths excluded
19	EPP	All, 103	10	
	EPP + RT	All, 65	14	
	EPP + RT	EP, 18	28	Pathologically node-negative
20	EPP	All, 177	10	Selected by PET-CT + mediastinoscopy
	Multimod	All, 207	20	Selected by PET-CT + mediastinoscopy
24	Doc + RT + C	All, 49	26	Also received interleukin-2

C, Chemotherapy; EPP, extrapleural pneumonectomy; Doc, decortication; RT, radiotherapy; EP, epithelial subtype; CT, computed tomography; PET, positron emission tomography.